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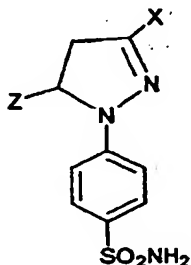
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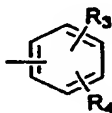
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(54) Title: **1-(4-SULFAMYLARYL)-3-SUBSTITUTED-5-ARYL-2-PYRAZOLINES AS INHIBITORS OF CYCLOOXYGENASE-2**



(I)



(II)

(57) Abstract: Compounds of formula (I) wherein: X is selected from the group consisting of trihalomethyl, C₁-C₆ alkyl, and a group of formula (II) wherein: R₃ and R₄ are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C₁-C₆ alkyl; C₁-C₆ alkoxy; carboxy; C₁-C₆ trihaloalkyl; and cyano; Z is selected from the group consisting of substituted and unsubstituted aryl; or a pharmaceutically acceptable salt thereof. The compounds are inhibitors of cyclooxygenase-2 activity. They are useful for treating cyclooxygenase-mediated disorders,

including, for example, inflammation, neoplastic disorders and angiogenesis-mediated disorders.

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1-(4-SULFAMYLARYL)-3-SUBSTITUTED-5-ARYL-2-PYRAZOLINES AS INHIBITORS OF CYCLOOXYGENASE-2

Cross-Reference to Related Application

5 The benefit of the filing date of U.S. provisional patent application Ser. No. and 60/139,416, filed June 16, 1999 is hereby claimed pursuant to 35 U.S.C. 119(e). The entire disclosure of the aforesaid provisional application is incorporated herein by reference.

Field of the Invention

10 The invention relates generally to anti-inflammatory drugs, and more particularly to novel compounds which inhibit the activity of cyclooxygenase-2.

Background of the Invention

15 The metabolites of arachidonic acid, such as prostaglandins, lipoxygenases and thromboxane products are produced in a wide variety of tissues and play a key role in several biological responses. Prostaglandins mediate both beneficial and undesirable biological reactions. The production of prostaglandins induces pain, swelling, heat and redness which are characteristic features of inflammation. The chronic inflammation associated with prostaglandin production leads to the breakdown of the injured tissue and angiogenesis. In pathologic chronic inflammation, normal tissues can be destroyed and the new blood vessel formation can support growth of abnormal tissue. Prostaglandins are also important for normal physiological processes in different organs. In the stomach, prostaglandins protect mucosa from acid. They also regulate

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blood flow and salt-water balance in the kidney. Prostaglandins are also important in platelets aggregation and participate in memory and other cognitive functions.

Prostaglandins are produced from cell membrane phospholipids by a cascade of enzymes. The enzymatic activities involve release of arachidonic acid from the cell membrane by phospholipase A₂, followed by the conversion of arachidonic acid to a common prostaglandin precursor, PGH₂, by cyclooxygenase (also called prostaglandin H synthase). PGH₂ is finally converted to various types of prostaglandins (PGE₁, PGE₂, PGI₂ or prostacyclin, PGF_{2α} and thromboxane) by cell-specific synthases.

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) block the formation of prostaglandins by inhibiting cyclooxygenase activity. They have analgesic, antipyretic and anti-inflammatory activities. However, chronic treatment with the available NSAIDs often leads to disruption of beneficial prostaglandin-mediated processes. The side effects associated with constant usage of NSAIDs include gastrointestinal (GI) irritation and formation of life-threatening GI ulcers.

A dramatic advance in the field of inflammation research came with discovery of multiple enzymes for each step of the prostaglandin synthase cascade. The research suggested that in some situations, such as inflammation, cyclooxygenase was inducible. The cyclooxygenase known at the time, cyclooxygenase-1 (COX-1), was clearly non-inducible or modulated by glucocorticoids. A second, inducible form of cyclooxygenase known as cyclooxygenase-2 (COX-2) was subsequently identified and cloned by several groups of investigators. COX-1 is the constitutive cyclooxygenase isoform and is mainly responsible for the synthesis of cytoprotective prostaglandins in the GI tract and the synthesis of thromboxane which triggers platelet aggregation in blood platelets. COX-2 is inducible and short lived except in the case of certain tumors

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where it is constitutively activated. COX-2 expression is stimulated in response to endotoxins, cytokines, hormones, growth factors and mitogens. These observations suggest that COX-1 and COX-2 serve different physiological and pathophysiological functions. Indeed, it has been suggested that COX-1 is responsible for endogenous basal release of prostaglandins and hence is important to the physiological functions of prostaglandins such as GI integrity and renal blood flow. On the other hand, it has been suggested that COX-2 is mainly responsible for the pathological effects of prostaglandins, where induction of the enzyme occurs in response to inflammatory agents, hormones, growth factors and cytokines. See, U.S. Pat. 5,604,253, incorporated herein by reference, for a discussion of the advantages of selective COX-2 inhibition. Principally, a selective COX-2 inhibitor is expected to possess similar anti-inflammatory, antipyretic and analgesic properties to a conventional NSAID but with reduced potential for gastrointestinal toxicity, and a reduced potential for renal side effects.

The differential tissue distribution of COX-1 and COX-2 provides an approach to develop selective inhibitors for COX-2 with reduced effect on COX-1, thereby preventing gastric side effects.

A number of selective COX-2 inhibitors have been reported. These include diaryl heterocyclics (Penning *et al.*, *J. Med. Chem.*, **40**, 1347-1365 (1997); acetoxyphenyl alkyl sulfides (Kalgutkar *et al.*, *J. Med. Chem.*, **41**, 4800-4818 (1998); methane sulfonanilides (Li *et al.*, *J. Med. Chem.*, **38**, 4897-4905 (1995); and tricyclic inhibitor classes (Wilkerson *et al.*, *J. Med. Chem.*, **38**, 3895-3901 (1995). U.S. Pat. 5,604,253 discloses N-benzylindol-3-yl propanoic acid derivatives as cyclooxygenase inhibitors.

What is needed are additional COX-2 inhibitors, particularly compounds which selectively inhibit the cyclooxygenase activity of COX-2 over COX-1.

Summary of the Invention

It is an object of the invention to provide compounds and pharmaceutical compositions thereof for inhibiting the biological activity of COX-2, in particular the cyclooxygenase activity of COX-2.

5 It is an object of the invention to provide for methods of treating disease conditions which are associated with undesired prostaglandin production and/or secretion.

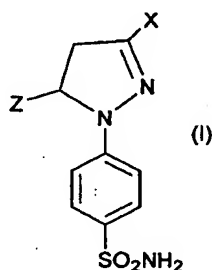
It is an object of the invention to provide for the treatment of cyclooxygenase-mediated disorders.

10 It is an object of the invention to provide compounds which selectively inhibit COX-2 over COX-1.

It is an object of the invention to provide methods for synthesizing compounds of the invention and intermediates thereof.

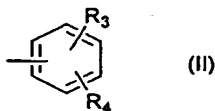
15 These and other objects of the invention shall become apparent from the following disclosure.

Compounds of formula I, and pharmaceutically acceptable salts thereof, are provided



wherein:

20 X is selected from the group consisting of C₁-C₆ trihalomethyl, preferably trifluoromethyl; C₁-C₆ alkyl; and an optionally substituted or di-substituted phenyl group of formula II:



- 5 -

wherein:

5 R₃ and R₄ are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C₁-C₆ alkyl, preferably C₁-C₃ alkyl; C₁-C₆ alkoxy, preferably C₁-C₃ alkoxy; carboxy; C₁-C₆ trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

10 Z is selected from the group consisting of substituted and unsubstituted aryl.

 The carbon chains in the alkyl and alkoxy groups which may occur in the compounds of the invention may be straight or branched. The expression "C₁-C₆ alkyl" thus extends to alkyl groups containing one, two, three, four, five or six carbons. The expression "C₁-C₆ alkoxy" thus
15 extends to alkoxy groups containing one, two, three, four, five or six carbons.

 The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term
20 "aryl" is intended to include not only aromatic systems containing only carbon ring atoms but also systems containing one or more non-carbon atoms as ring atoms. Such systems may be known as "heteroaryl" systems. The term "aryl" is thus deemed to include "heteroaryl".

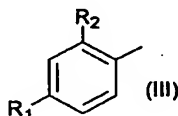
 Preferred aryl groups Z include phenyl and heteroaryl, which
25 may be substituted or unsubstituted. By "substituted" is meant any level of substitution, although mon- di- and tri-substitution are preferred. The substituents are independently selected. The substituents are preferably selected from the group consisting of halogen, particularly chlorine, fluorine and bromine; hydroxyl; nitro; C₁-C₆ alkyl, preferably C₁-C₃ alkyl, most

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preferably methyl; C₁-C₆ alkoxy, preferably C₁-C₃ alkoxy, most preferably methoxy; carboxy; C₁-C₆ trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano. Although mono-, di- and tri-substitution is preferred, full substitution, particularly when the aryl group is phenyl, is possible. According to one preferred embodiment, Z is phenyl, and is mono-, di-, tri-, tetra- or penta-substituted with halogen. The halogen atoms may be the same or different.

According to another embodiment, Z is an aryl group other than phenyl or substituted phenyl, and is particularly substituted or unsubstituted heteroaryl. Such heteroaryl radicals include, for example, pyridyl, particularly 2-, 3- and 4-pyridyl; thienyl, particularly 2- and 3-thienyl; furyl, particularly 2- and 3-furyl; indolyl, particularly 3-, 4-, 5-, 6-, 7- and 8-indolyl; benzothienyl, particularly 3-, 4-, 5-, 6-, 7- and 8-benzothienyl; benzofuryl, particularly 3-, 4-, 5-, 6-, 7- and 8-benzofuryl; imidazolyl, particularly 2- and 5-imidazolyl; pyrazolyl, particularly 3- and 5-pyrazolyl; 2-thiazolyl; 2-benzothiazolyl; quinoliny, particularly 2-, 3- and 4-quinoliny; and 4-(2-benzoxazolyl). Representative preferred substituted heteroaryl groups include 6-methyl-2-pyridyl, 5-halo-2-thienyl, 5-methyl-2-thienyl, 5-halo-2-furyl, 5-halo-3-furyl, 2,5-dimethyl-3-thienyl and 2,5-dimethyl-3-furyl.

According to one preferred embodiment of the invention, Z is an optionally 2- or 4-substituted (or 2-, 4-di-substituted) phenyl group of the formula III:



wherein R₁ and R₂ are independently selected from the group consisting of hydrogen; halogen, particularly fluorine, bromine and chlorine; hydroxyl; nitro; C₁-C₆ alkyl; C₁-C₆ alkoxy; and carboxy.

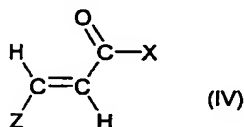
According to another preferred embodiment, wherein X is optionally mono- or di-substituted phenyl according to formula II, R₃ and R₄ are

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independently selected from the group consisting of hydrogen, halogen, hydroxyl; nitro; C₁-C₆ alkyl, C₁-C₆ alkoxy and carboxy, most preferably hydrogen, fluorine, bromine, chlorine, C₁-C₃ alkyl, C₁-C₃ alkoxy, hydroxy and nitro. When R₃ is hydrogen and R₄ is other than hydrogen, the preferred ring attachment position of R₄ is the 2- or 4- position, most preferably the 4-position. Where both R₃ and R₄ are other than hydrogen, the preferred positions of substitution are the 2- and 4-positions, or the 3- and 4-positions.

The invention is also directed to isolated optical isomers of compounds according to formula I or V. By "isolated" means a compound which has been substantially purified from the corresponding optical isomer(s) of the same formula. Preferably, the isolated isomer is at least about 80%, more preferably at least 90% pure, even more preferably at least 98% pure, most preferably at least about 99% pure, by weight.

The invention is also directed to novel intermediates of the formula



where X and Z are defined as above.

The invention is also directed to methods for preparing the aforesaid novel intermediates. A method for preparing a compound of formula IV comprises

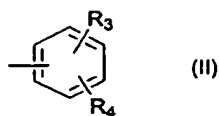
(a) reacting a ketone compound selected from the group consisting of

- (i) 1,1,1-trihaloacetone, preferably 1,1,1-trifluoroacetone; and
- (ii) a compound of the formula



wherein X is C₁-C₆ alkyl, or a radical of the formula

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wherein R_3 and R_4 are defined above;
with a compound of the formula



wherein Z is selected from the group consisting of substituted and unsubstituted aryl; and

5 (b) isolating a compound according to formula IV from the reaction products. According to a preferred embodiment, the reaction temperature is maintained in the range of from about 15°C to about 30°C, but higher temperatures are possible depending on the boiling points of the reactants.

An alternative method is provided for preparing the aforesaid intermediates of formula IV wherein X is trihalomethyl, preferably trifluoro-,
10 tribromo-, or trichloromethyl. The method comprises:

(a) reacting diethyl methylphosphonate with an N-phenyltrihaloacetimidoyl chloride and a compound of the formula

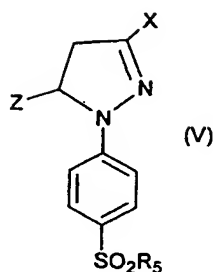


wherein Z is selected from the group consisting substituted and
15 unsubstituted aryl; and

(b) isolating a compound according formula IV wherein X is trihalomethyl from the reaction products.

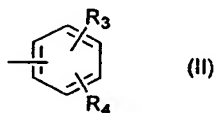
According to another embodiment of the invention, a compound of the formula V is provided:

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wherein:

X is selected from the group consisting of trihalomethyl, C₁-C₆ alkyl, and a group of formula II:



wherein:

R₃ and R₄ are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C₁-C₆ alkyl; C₁-C₆ alkoxy; carboxy; C₁-C₆ trihaloalkyl; and cyano;

Z is substituted or unsubstituted aryl, preferably substituted or unsubstituted heteroaryl; and

R₅ is selected from the group consisting of



wherein R₆ is C₁-C₆ alkyl and M is Na, K or Li; or a pharmaceutically acceptable salt thereof.

Methods are also provided for preparing compounds according to formula I, by reacting the formula IV intermediate, wherein X and Z are

defined as above, with 4-sulfamyl phenyl hydrazine or salt thereof; and isolating a compound according to formula I from the reaction products.

The invention is also directed to a pharmaceutical composition of one or more compounds of formula I in combination with a pharmaceutically effective carrier.

According to yet another embodiment of the invention, a method for treating a cyclooxygenase-mediated disease is provided comprising administering an effective amount of a compound according to formula I to an animal in need of such treatment. The expression "animal" is inclusive of human beings.

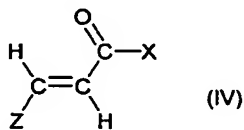
Description of the Figure

Fig.1 shows the inhibition of colorectal cancer cell colony growth in the presence of compounds of the invention, as compared to celecoxib.

Detailed Description of the Invention

The compounds of formula I are potent inhibitors of COX-2. COX-2 activity was demonstrated by a cell-free assay in which human recombinant COX-2 was incubated with test compound and [¹⁴C]-arachidonic acid. The resulting radiolabeled prostanoid compounds, i.e., the products of COX-2 reaction with arachidonic acid, were quantified.

The compounds of the invention may be prepared via an intermediate of formula IV:



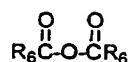
wherein X and Z are defined as above.

The compounds of formula I are prepared by reacting the intermediate of formula IV with sulfamyl phenyl hydrazine hydrochloride.

According to another embodiment of the invention a compound

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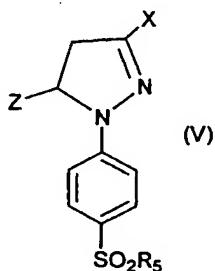
according to formula I may be further reacted with an anhydride of the formula



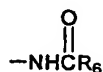
or an acylating compound of the formula



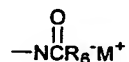
wherein R_6 is C_1 - C_6 alkyl, to form the corresponding sulfonamide, that is,
 5 a compound according to formula V:



wherein R_5 is



10 and R_6 is defined as above. The corresponding alkali metal salt, that is, a compound where R_5 is



and M is Na, K or Li, may be formed by reacting the above sulfonamide with an alkali hydroxide, selected from the group consisting of NaOH, KOH or LiOH.

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The following are general procedures for preparation of the formula I compounds or intermediates thereof:

Procedure 1: Synthesis of *trans*-1,1,1-trifluoro-4-aryl-3-buten-2-one intermediate

- 5 To a solution of 10% sodium hydroxide in ethanol (25 ml), 1,1,1-trifluoroacetone (10 mmol) is added and stirred at 15-20°C. To this a solution of the appropriate araldehyde (10 mmol)



- where Z is defined as above, is added and stirred vigorously for 4 hrs. The temperature of the reaction is maintained at 15-20°C throughout the reaction. The solution is then poured into ice water and acidified with concentrated hydrochloric acid. The resulting separated *trans*-1,1,1-trifluoro-4-aryl-3-buten-2-one of formula IV (X=CF₃) is extracted with ether dried over anhydrous MgSO₄. Evaporation of the dried ethereal layer yields the *trans*-1,1,1-trifluoro-4-aryl-3-buten-2-one which is purified by recrystallization.

Procedure 1A: Alternative synthesis of *trans*-1,1,1-trifluoro-4-aryl-3-buten-2-one intermediate

- To a cooled solution of (-70°C) lithium diisopropylamide (10 mmol), diethyl methylphosphonate (5 mmol) is added. After the mixture is stirred for 30 minutes at -70°C, N-phenyltrifluoroacetimidoyl chloride (5 mmol) is gradually added and stirring is continued at -70°C for 1 hour. The appropriate araldehyde (5mmol)



where Z is defined as above, is added dropwise for 10 minutes. The resulting mixture is warmed to room temperature over 2 hours and then

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stirred overnight. Then 20 ml of dilute hydrochloric acid is added and stirred at room temperature for 4 hours. The solution is extracted thrice with diethyl ether (20 ml each time) and washed successively with 5% sodium bicarbonate and brine until the pH of the solution is 6. The ethereal
 5 layer is separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield crude trans -1,1,1-trifluoromethyl -4-aryl-3-buten-2-one. The product is purified either by column chromatography or by recrystallization.

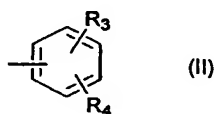
The appropriate 1,1,1-trihaloacetone can be substituted for 1,1,1-trifluoroacetone in Procedure 1 to provide other trans-1,1,1-trihalo-4-aryl-3-buten-2-one intermediate. Similarly, other N-phenyltrihaloacetimidoyl
 10 chlorides can be substituted for N-phenyltrifluoroacetimidoyl chloride in Procedure 1A to produce other trans-1,1,1-trihalo-4-aryl-3-buten-2-one intermediates.

15 **Procedure 2: Synthesis of *trans*-1-(alkyl or optionally substituted aryl)-3-aryl-2-propen-1-one intermediate**

To a solution of 10% sodium hydroxide in ethanol (25 ml), a ketone of the formula



20 wherein X is C₁-C₆ alkyl (20 mmol), or a radical of formula II



wherein R₃ and R₄ are defined as above (10 mmol), is added and stirred at 15-20°C. To this a solution of the appropriate araldehyde (10 mmol)

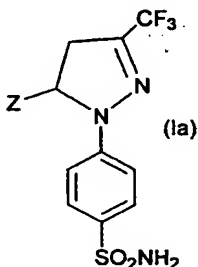


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where Z is defined as above, is added and stirred vigorously for 4 hours. The temperature of the reaction is maintained at 15-20°C throughout the reaction. The solution is then poured into ice water and acidified with concentrated hydrochloric acid. The resulting separated *trans*-1-(alkyl or optionally substituted aryl)-3-aryl-2-propen-1-one of formula IV (X = C₁-C₆ alkyl, or radical of formula II) is extracted with ether dried over anhydrous MgSO₄. Evaporation of the dried ethereal layer yields the *trans*-1-(alkyl or optionally substituted aryl)-3-aryl-2-propen-1-one, which is purified by distillation or recrystallization.

10 **Procedure 3: Synthesis of 1-(4-sulfamylaryl)-3-trifluoromethyl-5-aryl-2-pyrazoline**

To a solution of a *trans*-1,1,1-trifluoro-4-aryl-3-butene-2-one (5 mmol) of formula IV (X = CF₃) in absolute methanol is added 4-sulfamyl phenyl hydrazine hydrochloride (6 mmol). The mixture is refluxed with stirring overnight on a hot plate with a stirrer. The solution is cooled and poured onto crushed ice and solid material is separated by filtration. Recrystallization of the solid material with appropriate solvent yields the pure 1-(4-sulfamylaryl)-3-trifluoromethyl-5-aryl-2-pyrazoline of formula Ia:



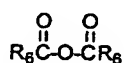
Procedure 4: Synthesis of 1-(4-sulfamylaryl)-3-(alkyl or optionally substituted aryl)-5-aryl-2-pyrazoline

To a solution of a *trans*-1-(alkyl or optionally substituted aryl)-3-aryl-2-propen-1-one (5 mmol) of formula IV in absolute methanol is added 4-sulfamyl phenyl hydrazine hydrochloride (6 mmol). The mixture is refluxed with stirring overnight on a hot plate with a stirrer. The solution is cooled and poured onto crushed ice and solid material is separated by filtration. Recrystallization of the solid material with appropriate solvent yields the pure 1-(4-sulfamylaryl)-3-(alkyl or optionally substituted aryl)-5-aryl-2-pyrazoline of formula I, wherein X is defined as in Procedure 2.

Procedure 5: Synthesis of N-[4-(5-Aryl-3-trifluoromethylpyrazolin-1-yl)phenylsulfonyl]acetamide

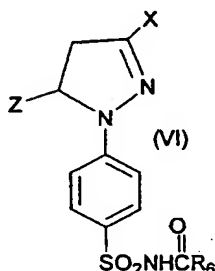
To a solution of a 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-aryl-2-pyrazoline (10 mmol) in tetrahydrofuran (40 ml), acetic anhydride (20 mmol), 4-dimethylaminopyridine (10 mmol) and triethylamine (11 mmol) is added and stirred for 16 hours at room temperature. The reaction mixture is then poured into water (100 ml) and extracted with ethyl acetate. The ethyl acetate layer is separated, washed successively with water, brine and then dried over anhydrous sodium sulfate. The dried organic layer is filtered and evaporated under reduced pressure to yield crude N-[4-(5-aryl-3-trifluoromethylpyrazolin-1-yl)phenylsulfonyl]acetamide. Recrystallization from a mixed solvent yields a pure compound.

Other sulfonamides may be prepared by substituting an anhydride of the formula



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where R_6 is C_1 - C_8 alkyl, for acetic anhydride in Procedure 5 to yield compounds of the formula VI, wherein X is trifluoromethyl:



Procedure 6: Synthesis of N-[4-(5-Aryl-3-trifluoromethylpyrazolin-1-yl)phenylsulfonyl]acetamide sodium salt

5

To a solution of N-[4-(5-aryl-3-trifluoromethylpyrazolin-1-yl)phenylsulfonyl]acetamide (5 mmol) in ethanol (100ml), sodium hydroxide (5 mmol in 20 ml of water) is added and stirred for 5 hours. The solution is then concentrated in vacuum to give a solid hydrated sodium salt of 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-aryl-2-pyrazoline.

10

Salts of other sulfonamides may be prepared in the same manner by substituting the appropriate amide according to formula V as the starting compound.

Procedure 7: Synthesis of N-[4-(5-Aryl-3-[alkyl or optionally substituted aryl]pyrazolin-1-yl)phenylsulfonyl]acetamide

15

N-[4-(5-Aryl-3-[alkyl or optionally substituted aryl]pyrazolin-1-yl)phenylsulfonyl]acetamides according to formula V ($X = C_1$ - C_8 alkyl or optionally substituted or di-substituted phenyl) are prepared according to Procedure 5, substituting the appropriate 1-(4-sulfamylphenyl)-3-(alkyl or optionally substituted phenyl)-5-aryl-2-pyrazoline for 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-aryl-2-pyrazoline as the starting material.

20

In similar fashion, sulfonamides according to formula V ($X = C_1-C_6$ alkyl or optionally substituted or di-substituted phenyl), other than acetamides, may be prepared by substituting the appropriate anhydride for acetic anhydride in Procedure 5. These compounds may be converted to salts according to Procedure 6.

The compounds of the invention preferably are characterized by a selectivity ratio for COX-2 inhibition over COX-1 inhibition of at least about 50, more preferably at least about 100. COX inhibition may be determined *in vitro* by enzyme assays well-known to those skilled in the art, such as the enzyme assay method described later herein.

The compounds of the present invention may take the form or pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts", embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Where reference is made to "compound of formula I (or formula V)" or a "compound of the invention", it is understood that pharmaceutically acceptable salts are also included. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, salicylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, beta-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable

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pharmaceutically acceptable base addition salts of compounds of formula I include metallic salts made from calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of formula I or V by reacting, for example, the appropriate acid or base with the compound of formula I or V.

The compounds of the present invention may be administered in the form of a pharmaceutical composition, in combination with a pharmaceutically acceptable carrier. The active ingredient in such formulations may comprise from 0.1 to 99.99 weight percent. By "pharmaceutically acceptable carrier" is meant any carrier, diluent or excipient which is compatible with the other ingredients of the formulation and to deleterious to the recipient.

The compounds of the invention may be administered to individuals (animals, most particularly mammals including humans) afflicted with any disorder characterized by undesirable prostaglandin production resulting from cyclooxygenase activity, particularly COX-2 activity ("cyclooxygenase-mediated disorder"). In particular, the compounds of the invention are believed useful in treating inflammation and inflammation-related disorders, by administering to a subject having or susceptible to such inflammation or inflammation-related disorder and effective amount of a compound according to formula I. Inflammation is associated with a variety of disease conditions. For a list of such disease conditions treatable by cyclooxygenase inhibitors, and COX-2 inhibitors in particular, see U.S. Patents 5,604,253 and 5,908,852, the entire disclosures of which are incorporated herein by reference. Such conditions include, for example, arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such conditions further include rheumatic fever, symptoms associated with

influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, gout and ankylosing spondylitis, bursitis, and following surgical and dental procedures. The compounds of the invention are
5 believed useful as analgesics for treating or alleviating all forms of pain. The compounds are believed useful in the treatment of other disorders including asthma, bronchitis, tendinitis, bursitis; skin related conditions such as psoriasis, eczema, burns and dermatitis; gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel
10 syndrome and ulcerative colitis and for the prevention of colorectal cancer; the treatment of inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis,
15 gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds of the invention are believed useful as antipyretics for the treatment of fever.

In addition, compounds of the invention may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be
20 used in the treatment of cancer. In particular, the present invention provides a method for treating or preventing a neoplasia that produces a prostaglandin in a subject in need of such treatment or prevention, the method comprises treating the subject with a therapeutically effective amount of a compound of formula I or V. The term "neoplasia" includes
25 neoplasia that produce prostaglandins or express a cyclooxygenase, including both benign and cancerous tumors, growths and polyps. Neoplasias believed treatable with cyclooxygenase inhibitors are discussed in U. S. Pat. 5,972,986, the entire disclosure of which is incorporated herein by reference. The compounds may be used to inhibit the growth or
30 an established neoplasm, i.e., to induce regression, or to prevent or delay the onset of the neoplasm.

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According to U.S. Pat. 5,972,986, neoplasias that produce prostaglandins, and which are therefore believed treatable with the compounds of the invention, include brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body.

The compounds of the invention may also be useful in the treatment of angiogenesis-mediated disorders. Thus, a method for treating, inhibiting or delaying the onset of an angiogenesis-mediated disorder in a subject is provided comprising administering to a subject in need of such treatment an effective amount of a compound according to the present invention. Angiogenesis-mediated disorders which may be treatable with cyclooxygenase inhibitors are discussed in U. S. Pat. 6,025,353, the entire disclosure of which is incorporated herein by reference. According to U. S. Pat. 6,025,353, such disorders include, for example, metastasis, corneal graft rejection, ocular neovascularization, retinal neovascularization, diabetic retinopathy, retrolental fibroplasia, neovascular glaucoma, gastric ulcer, infantile hemangiomas, angiofibroma of the nasopharynx, avascular necrosis of bone, and endometriosis.

The compounds may be administered by any route, including oral and parenteral administration. Parenteral administration includes, for example, intravenous, intramuscular, intraarterial, intraperitoneal, intranasal, rectal, or subcutaneous administration. The active agent is preferably administered with a pharmaceutically acceptable carrier selected on the basis of the selected route of administration and standard pharmaceutical practice.

The active agent may be formulated into dosage forms according to standard practices in the field of pharmaceutical preparations. See Alphonso Gennaro, ed., *Remington's Pharmaceutical Sciences*, 18th Ed., (1990) Mack Publishing Co., Easton, PA. Suitable dosage forms may
5 comprise, for example, tablets, capsules, solutions, parenteral solutions, troches, suppositories, or suspensions.

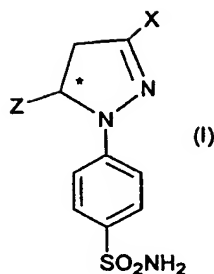
For parenteral administration, the active agent may be mixed with a suitable carrier or diluent such as water, an oil, saline solution, aqueous dextrose (glucose) and related sugar solutions, or a glycol such as
10 propylene glycol or polyethylene glycol. Solutions for parenteral administration preferably contain a water soluble salt of the active agent. Stabilizing agents, antioxidizing agents and preservatives may also be added. Suitable antioxidizing agents include sulfite, ascorbic acid, citric acid and its salts, and sodium EDTA. Suitable preservatives include
15 benzalkonium chloride, methyl- or propyl-paraben, and chlorbutanol.

For oral administration, the active agent may be combined with one or more solid inactive ingredients for the preparation of tablets, capsules, or other suitable oral dosage forms. For example, the active agent may be
combined with carboxymethylcellulose calcium, magnesium stearate,
20 mannitol and starch, and then formed into tablets by conventional tableting methods.

The specific dose of compound according to the invention to obtain therapeutic benefit will, of course, be determined by the particular circumstances of the individual patient including, the size, weight, age and
25 sex of the patient, the nature and stage of the disease, the aggressiveness of the disease, and the route of administration. For example, a daily dosage of from about 0.01 to about 150 mg/kg/day may be utilized. Higher or lower doses are also contemplated.

The compounds of the present invention are optically active due to
30 the presence of a chiral carbon atom at position 5 of the pyrazoline nucleus:

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Other chiral carbon atoms may also be present. The present invention is meant to comprehend diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof. Isolated optical isomers may be purified from racemic mixtures by well-known chiral separation techniques. According to one such method, a racemic mixture of a compound having the structure of formula I or V, or chiral intermediate thereof, is separated into 99% wt.% pure optical isomers by HPLC using a suitable chiral column, such as DAICEL CHIRALPAK AD (Daicel Chemical Industries, Ltd., Tokyo, Japan). This column contains a packing of amylose tris(3,5-dimethylphenyl) carbamate coated on a 10 μ m silica-gel substrate. The column has a size of 250 x 4.6 mm (L x I.D.). The column is operated according to the manufacturer's instructions. A flow rate should be maintained that will result in column pressures of less than 430 psi (30 kg/cm²). A typical flow rate is 1.0 ml/min. The operating temperature range is 0°C - 40°C. The maximum operating pressure is 1200 psi. One suitable mobile phase system is hexane/2-propanol (100/0 to 0/100 v/v). A typical hexane/2-propanol mobile phase is hexane/2-propanol (90/10 v/v). Another suitable mobile phase system is hexane/ethanol (100/0 to 85/15 v/v), (40/60 to 0/100 v/v). Suitable mobile phase modifiers include N,N-diethylamine for a basic sample, and trifluoroacetic acid for an acidic sample.

The practice of the invention is illustrated by the following non-limiting examples.

Example 1

1- (4-sulfamylphenyl)-3-trifluoromethyl-5-phenyl-2-pyrazoline

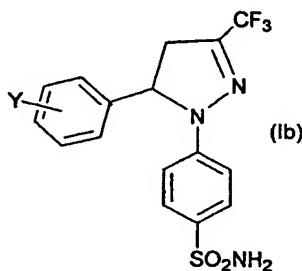
A. *Trans*-1,1,1-trifluoro-4-phenyl-3-buten-2-one was prepared according to Procedure 1 from 1,1,1-trifluoroacetone and benzaldehyde.

5 B. A solution of *trans*-1,1,1-trifluoro-4-phenyl-3-buten-2-one (5 mmol) and 4-sulfamylphenyl hydrazine hydrochloride (6 mmol) was subjected to Procedure 3. The title compound was obtained in 73% yield, m.p. 132-135°C; C, H analysis ($C_{18}H_{15}SO_2N_4F_3 \cdot H_2O$):

		<u>%C</u>	<u>%H</u>	<u>%N</u>
10	Calcd.	50.70	4.01	13.13
	Found	49.90	3.95	13.13

Table 1, Examples 2-23, lists additional compounds which are prepared by reacting a *trans*-1,1,1-trifluoro-4-(substituted)phenyl-3-buten-2-one (5 mmol) and 4-sulfamylphenyl hydrazine hydrochloride according to
15 Procedure 3.

Table 1



	<u>Example</u>	<u>Y</u>
	2	2-Cl
	3	3-Cl
20	4	4-Cl
	5	2-F
	6	3-F
	7	4-F
	8	4-Br
25	9	2-Cl,4-F

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	10	2,4-Cl ₂
	11	3,4-Cl ₂
	12	3-Cl,4-F
	13	3,4-F ₂
5	14	2,3-Cl ₂
	15	2-CH ₃
	16	4-CH ₃
	17	2-OCH ₃
	18	4-OCH ₃
10	19	4-C ₂ H ₅
	20	4-CF ₃
	21	4-OH
	22	4-NO ₂
	23	4-COOH

15

Example 24**1- (4-sulfamylphenyl)-3-trifluoromethyl-5-(3-indolyl)-2-pyrazoline**

A. *Trans*-1,1,1-trifluoro-4-(3-indolyl)-3-buten-2-one was prepared according to Procedure 1 from 1,1,1-trifluoroacetone and 3-indolyl carboxaldehyde.

20

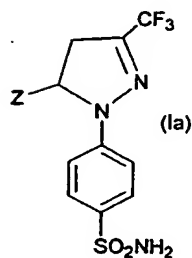
B. A solution of *trans*-1,1,1-trifluoro-4-(3-indolyl)-3-buten-2-one (5 mmol) and 4-sulfamylphenyl hydrazine hydrochloride (6 mmol) was subjected to Procedure 3. The title compound was obtained in 82% yield, m.p. 178-180°C; C, H analysis (C₁₆H₁₄SO₂N₄F₃):

		<u>%C</u>	<u>%H</u>	<u>%N</u>
25	Calcd.	52.03	3.82	11.37
	Found	51.91	3.84	11.15

Table 2, Examples 25-30, lists additional compounds which are prepared by reacting *trans*-1,1,1-trifluoro-4-aryl-3-buten-2-one and 4-sulfamylphenyl hydrazine hydrochloride according to Procedure 3.

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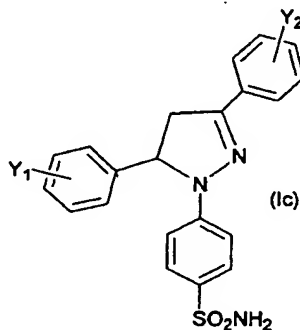
Table 2



Example	<u>Z</u>
25	2-furyl
26	2-thienyl
27	2-pyridyl
28	3-pyridyl
29	4-pyridyl
30	2-benzofuryl

Table 3, Examples 31-40, lists additional compounds which were prepared according to Procedures 2 and 4.

Table 3

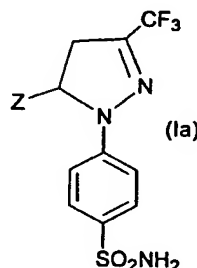


Example	<u>Y₁</u>	<u>Y₂</u>	<u>M.P. (°C)</u>
31	H	4-CH ₃ O	220-221
32	H	4-Cl	208-210
33	H	4-Br	206-207
34	4-F	4-F	188-190
35	4-Cl	4-F	212-213
36	4-CH ₃	4-F	226-227
37	4-Cl	4-Cl	217-219
38	4-CH ₃ O	H	193-194
39	4-CH ₃ S	4-CH ₃	204-206
40	4-CH ₃ SO ₂	4-CH ₃	250-252

Cyclooxygenase Enzyme Assay

Compounds were tested for inhibitory activity against COX-1 and COX-2. The compounds of Examples 1 and 24 had the highest selectivity for inhibiting COX-2.

5 Cyclooxygenase activity of ovine COX-1 (Oxford Biomedical Research Inc.) and human recombinant COX-2 (Oxford Biomedical Research Inc.) was assayed by a thin layer chromatography (TLC) method as follows. All inhibitors were dissolved in dimethyl sulfoxide to a stock solution of 5mM. Human recombinant COX-2 (3 units) or ovine COX-1 (15
10 units) was incubated with inhibitors at several concentrations in a solution containing 100 mM Tris-HCl, pH7.8, 500 μ M phenol and hematin for 90 to 120 minutes at room temperature (24°C). In controls, equal volumes of DMSO without drug were added to the incubation mixture. After incubation for 90-120 minutes, [1-¹⁴C] arachidonic acid (50 μ M, 51mCi/mmol) (DuPont
15 NEN) was added and incubated at 37°C for 2 minutes. The reaction was terminated by extraction with 1 ml of ethyl acetate. The ethyl acetate layer was transferred into a fresh tube and evaporated to dryness in a Speedvac vacuum dryer. The contents of the tubes were reconstituted in 20 ml of ethyl acetate and spotted on a TLC plate (J.T. Baker, Phillipsburg, NJ) and
20 developed in a mobile phase containing chloroform/methanol (95:5) at 4°C. Radiolabeled prostanoid compounds (the products of COX enzymatic reaction with radiolabeled arachidonic acid substrate) were quantitated with a radioactivity scanner (Fuji, Phosphorimager). The percentage of total products observed at different inhibitor concentrations was divided by the
25 percentage of the products observed for protein samples pre incubated for the same time with DMSO. The results are shown in Table 4. The Example 1 and 2 compounds are more than one thousand times more active in inhibiting COX-2 compared to COX-1.

Table 4: Inhibition of Cyclooxygenase Activity

		IC ₅₀ (μM)	
5	<u>Ex.</u>	<u>Z</u>	<u>COX-2</u>
			<u>COX-1</u>
	1	C ₆ H ₅	0.10
	24	3-indolyl	0.078
			>100
			>100

Soft Agar Assay

The Example 1 and 24 compounds were compared to the COX-2 inhibitor celecoxib in inhibiting the growth of DLD-1 cells in soft agar. DLD-1 cells are human colorectal carcinoma cells that overexpress COX-2. DLD-1 cells grow in soft agar and form tumors in nude mice. The soft agar assay was performed as follows. A layer of bottom agar (8% noble agar) was placed onto 60 mm² tissue culture dishes. The tumor cells were trypsinized from normal growth flasks while in exponential growth. The cells were counted by using a hemacytometer and 1.0 x 10⁵ cells were placed into the top agar mixture containing growth medium, 4% noble agar and various concentrations of drugs. The concentration range was normally between 10 μM to 75 μM. The cells were not refed during the assay system; therefore, the cells were treated with one dose of the agents. The plates were stained 20 days later with a 0.05% (w/v) nitroblue tetrazolium solution (which stains only viable cells) for 48 hours. The results are shown in Fig. 1, the y-axis being the percent of cell colonies remaining in comparison to untreated control cells. Even at the highest

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concentration tested, celecoxib obtained only about partial inhibition, compared to 100% for the compounds of the invention.

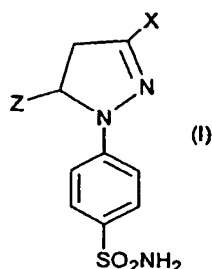
All references cited herein are incorporated herein by reference.

5 The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indication the scope of the invention.

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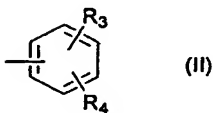
CLAIMS

1. A compound of the formula:



wherein:

- X is selected from the group consisting of trihalomethyl, C₁-C₆ alkyl,
 5 and a group of formula II:



wherein:

- R₃ and R₄ are independently selected from the group
 consisting of hydrogen; halogen; hydroxyl; nitro; C₁-C₆ alkyl;
 10 C₁-C₆ alkoxy; carboxy; C₁-C₆ trihaloalkyl; and cyano;

Z is selected from the group consisting of substituted and
 unsubstituted aryl; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein Z is selected from
 the group consisting of substituted and unsubstituted heteroaryl; or a
 15 pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 wherein Z is selected from
 the group consisting of substituted and unsubstituted indolyl, furyl, thienyl,
 pyridyl, benzofuryl, benzothienyl, imidazolyl, pyrazolyl, thiazolyl,
 benzothazolyl, quinolinyl, and 4-(2-benzyloxazolyl); or a pharmaceutically

acceptable salt thereof.

4. A compound according to claim 4 wherein Z is 3-indolyl; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1 wherein X is trifluoromethyl.

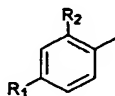
5 6. A compound according to claim 1 wherein X is a group according to formula II wherein R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C_1 - C_6 alkyl; C_1 - C_6 alkoxy; carboxy; C_1 - C_6 trihaloalkyl; and cyano; or a pharmaceutically acceptable salt thereof.

10 7. A compound according to claim 6 wherein R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C_1 - C_6 alkyl; C_1 - C_6 alkoxy; and carboxy; or a pharmaceutically acceptable salt thereof.

15 8. A compound according to claim 7 wherein Z is selected from the group consisting of unsubstituted phenyl; and mono-, di- and tri-substituted phenyl.

9. A compound according to claim 8 wherein Z is phenyl substituted with one or more of halogen, hydroxyl, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or carboxy; or a pharmaceutically acceptable salt thereof.

20 10. A compound according to claim 9 wherein Z is the group



wherein R_1 and R_2 are independently selected from the group consisting of

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hydrogen, fluorine, bromine, chlorine, C₁-C₃ alkyl, C₁-C₃ alkoxy, hydroxyl and nitro; or a pharmaceutically acceptable salt thereof.

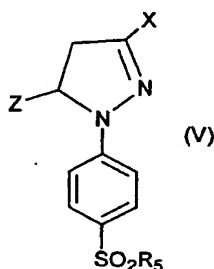
11. A compound according to claim 7 wherein Z is substituted or unsubstituted indolyl, furyl, thienyl, pyridyl or benzofuryl; or a
5 pharmaceutically acceptable salt thereof.

12. A compound according to claim 11 wherein 11 is 3-indolyl; or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 1 which is 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-phenyl-2-pyrazoline; or a
10 pharmaceutically acceptable salt thereof.

14. The compound according to claim 1 which is 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-(3-indolyl)-2-pyrazoline; or a pharmaceutically acceptable salt thereof.

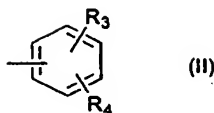
15. A compound of the formula V:



wherein:

X is selected from the group consisting of trihalomethyl, C₁-C₆ alkyl, and a group of formula II:

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wherein:

R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C_1 - C_6 alkyl;

5

C_1 - C_6 alkoxy; carboxy; C_1 - C_6 trihaloalkyl; and cyano;

Z is substituted or unsubstituted heteroaryl; and

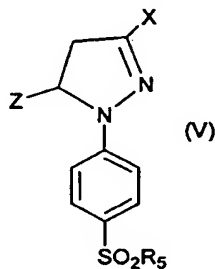
R_5 is selected from the group consisting of



wherein R_6 is C_1 - C_6 alkyl and M is Na, K or Li; or a pharmaceutically acceptable salt thereof.

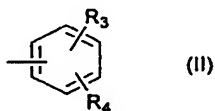
10

16. A compound of the formula V:



wherein:

X is a group of formula II:



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wherein:

R_3 and R_4 are independently selected from the group consisting of hydrogen; halogen; hydroxyl; nitro; C_1 - C_6 alkyl; C_1 - C_6 alkoxy; carboxy; C_1 - C_6 trihaloalkyl; and cyano;

5 Z is selected from the group consisting of substituted and unsubstituted aryl; and

R_5 is selected from the group consisting of



wherein R_6 is C_1 - C_6 alkyl and M is Na, K or Li; or a pharmaceutically acceptable salt thereof.

10 17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims 1, 15 or 16, or a pharmaceutically acceptable salt thereof.

15 18. A method for treating a cyclooxygenase-mediated disorder comprising administering to a patient in need of such treatment an effective amount of a compound according to any of claims 1, 15 or 16, or a pharmaceutically acceptable salt thereof.

20 19. A method for treating inflammation or an inflammation-mediated disorder comprising administering to a subject in need of such treatment an effective amount of a compound according to any of claims 1, 15 or 16, or a pharmaceutically acceptable salt thereof.

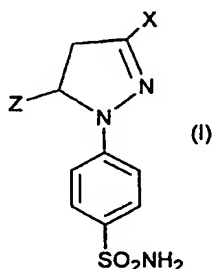
20 20. A method for treating a neoplasia comprising administering to a subject in need of such treatment an effective amount of a compound according to any of claims 1, 15 or 16, or a pharmaceutically acceptable

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salt thereof.

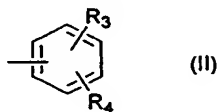
21. A method for treating an angiogenesis-mediated disorder administering to a subject in need of such treatment an effective amount of a compound according to any of claims 1, 15 or 16, or a
5 pharmaceutically acceptable salt thereof.

22. A method for producing a compound of formula I



wherein:

the group X is selected from the group consisting of trihalomethyl, C₁-C₆ alkyl, and a radical of formula II:



10 wherein:

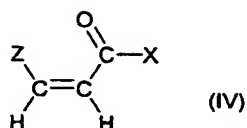
wherein R₃ and R₄ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, C₁-C₆ alkyl, C₁-C₆ alkoxy; carboxy; C₁-C₆ trihaloalkyl; and cyano; and

Z is selected from the group consisting of substituted and
15 unsubstituted aryl;

the method comprising:

(a) reacting a compound of the formula IV

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wherein X and Z are so defined;

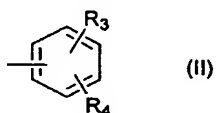
with 4-sulfamyl phenyl hydrazine or salt thereof; and

(b) isolating a compound according to formula I from the reaction products.

5 23. A method according to claim 22 wherein Z is substituted or unsubstituted heteroaryl.

24. A method according to claim 22 wherein X is a radical of formula II.

10 25. A method according to claim 22 wherein the group X in the reactant compound of formula II is selected from the group consisting of trifluoromethyl, C₁-C₆ alkyl, and a radical of formula II:



wherein:

wherein R₃ and R₄ are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, C₁-C₆ alkyl, C₁-C₆ alkoxy; and carboxy.

15 26. An isolated optical isomer of a compound according to any of claims 1, 15 or 16, or a pharmaceutically acceptable salt thereof.

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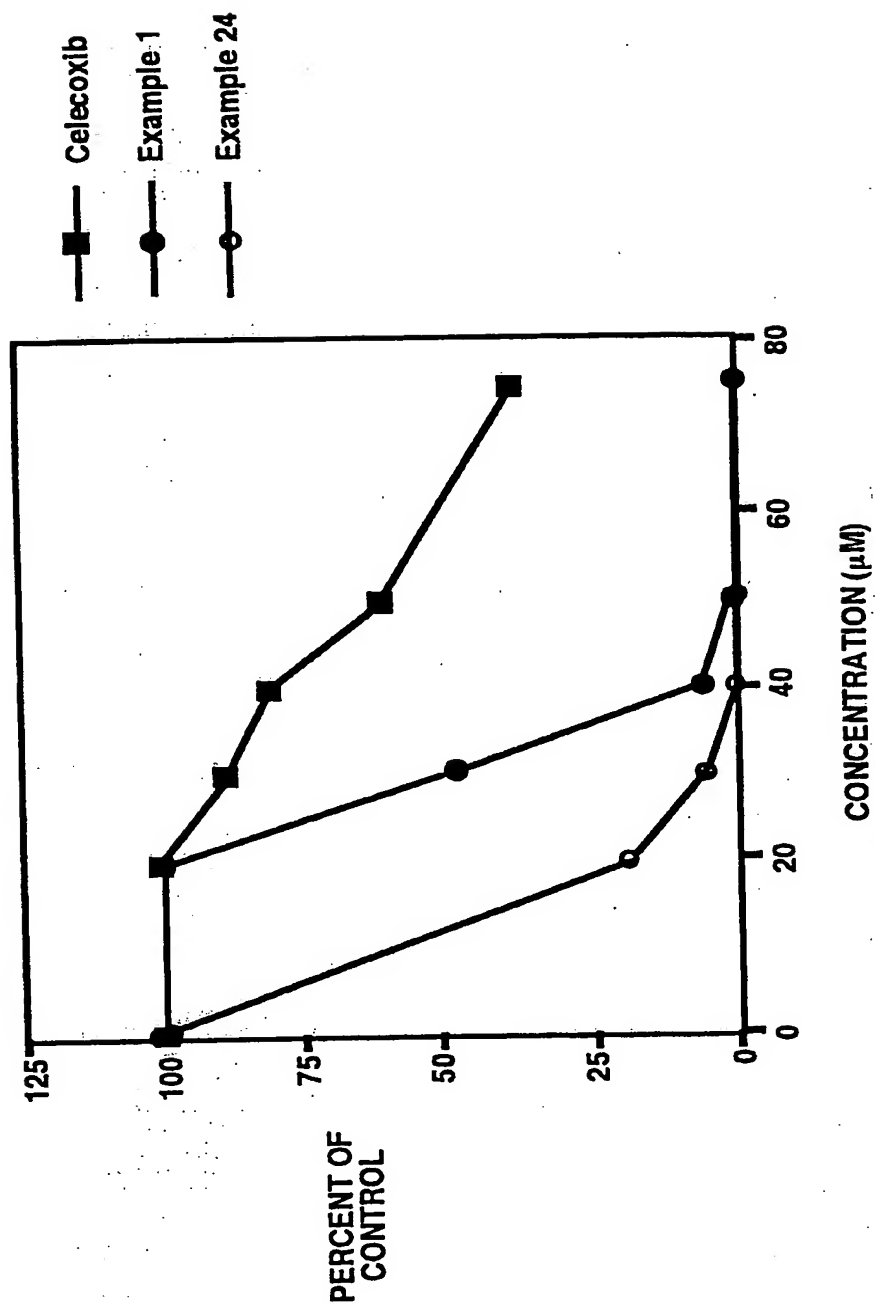


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16656

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/415; C07D 231/12

US CL : 514/403; 548/379.7

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/403; 548/379.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,865,816 A (H. MENGLER) 11 February 1975(11/02/75), see entire document, especially columns 1-4 and the claims.	1-26
X,P	Database CAS ONLINE on STN, Columbus, Ohio, AN 1999:78401, doc no. 132:12302, Cuberes-Altisent et al., 'Diarylpyrazoles', WO 99/62884, 99/12/09.	1-26
X	Database CAS ONLINE on STN, Columbus, Ohio, AN 1992:591744, Doc no. 117:191744, FAIDALLAH et al., 'Trisubstituted pyrazoles', Pak. J. Sci. Ind. Res. , 35(1-2), 8-13, 1992.	1-26

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents.	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

25 JULY 2000

Date of mailing of the international search report

03 AUG 2000

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